CLOSED-LOOP FEEDBACK CONTROL OF PROPOFOL ANAESTHESIA BY QUANTITATIVE EEG ANALYSIS IN HUMANS

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The electroencephalogram (EEG) has been used as a measure of drug action of anaesthetic compounds on the brain [1, 2]. More recent investigations include spectral EEG values to establish pharmacokinetic-pharmacodynamic models describing the drug input-effect relationship.

If the EEG correlates well with common clinical signs of depth of anaesthesia it might be used for control of anaesthesia. Median frequency of the EEG power spectrum (50% quantile) decreases as depth of anaesthesia increases. For etomidate [3], methohexitone [4] and isoflurane in nitrous oxide [5], median EEG frequencies less than 5 Hz were associated with unconsciousness as defined by non-responsiveness to verbal commands.

Appropriate rate control of drug delivery is a prerequisite to induce and maintain anaesthesia. Programmed schemes of drug administration need an adjustment for the individual subject and the varying nociceptive stimuli during surgery. Closed-loop feedback control methods [6,7] compare the set-point of the control variable with the value actually measured to modify rate of drug delivery. When applied to a pharmacological model, this comparison is used not only to correct dosing but also to update and individualize the model parameters. This method is commonly referred to as model based, adaptive feedback control. It has been applied recently to the control of methohexitone anaesthesia in volunteers [4].

In the present study, we have examined the applicability of model based, adaptive feedback control of propofol by quantitative EEG analysis in volunteers and compared this with the previous study of methohexitone.

**SUMMARY**

Propofol was administered for 2 h to 11 volunteers by an adaptive feedback control algorithm based on quantitative EEG analysis. Median EEG frequency served as the control variable. The range 2–3 Hz was chosen as the target range of control. During the feedback period, volunteers did not respond to commands and eyelash reflex was abolished. An average median frequency of 2.5 (SD 0.3) Hz was obtained by administering propofol 1452 (262) mg within 2 h. Time to recovery was 17.9 (8.0) min. Compared with a study with methohexitone using the same approach, the relative potency of propofol was 0.72. The mean recovery time was less than half that observed after methohexitone.

**SUBJECTS AND METHODS**

Eleven volunteers (24–31 yr, 54–87 kg, 162–197 cm) were studied after their informed written consent and institutional approval were obtained. After placing a cannula in a forearm vein and installing clinical monitoring, the baseline EEG was recorded. Four EEG leads \((C_z-O_{i1}, C_z-O_{i2})\) were amplified (Mingograph Junior, Siemens) and recorded on magnetic tape (PR 2200, Ampex). The lower impedance, was used for deriving the feedback signal.

Before induction of anaesthesia, the volunteers listened to music via earphones to smooth induction of anaesthesia and to lessen the awareness of the start of infusion. After recording the baseline...
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EEG, feedback control of propofol was instituted and maintained for 2 h. During the feedback control period, volunteers were exposed randomly to stimulation consisting of six types of stimuli: acoustic sensations, verbal commands, cold stimuli, pin pricks, and testing of eyelash and corneal reflexes, approximately every 1.5 min. Blood samples from a capillary in the ear lobe were taken every 20 min for measurement of gas tensions.

EEG analysis

The filter settings of the EEG amplifier were 0.3 s and 70 Hz. Before A-D conversion, the signal was analog filtered between 0.5 and 32 Hz, segmented into epochs of 8.192 s, and digitized at a rate of 125 Hz with 12-bit A-D resolution. For each epoch, the power spectrum between 0.5 and 32 Hz was calculated using common Fast-Fourier-Transformation (FFT) algorithms from which the median EEG frequency (50% quantile) of the power spectrum was derived. In addition, off-line analysis included calculation of fractional power in the frequency bands 0.5–2 Hz, > 2–5 Hz, > 5–8 Hz, > 8–13 Hz, > 13–32 Hz, and mean amplitude. For data smoothing, a moving average of nine epochs was performed.

Administration device and algorithm

Two infusion pumps (IP 4, Vickers) were attached in parallel to the computer (Eurocom 3, Eltec) by bypassing the digital switches electronically. The maximum rate of propofol administration was thus confined to 33.3 mg min⁻¹. The start of the automatic feedback control was preceded by a 4-min infusion of propofol at maximum rate. The subsequent rates of propofol infusion were determined on the basis of the feedback signal and the pharmacokinetic–dynamic model used for propofol. According to previous work [8] a linear two-compartment model was used to describe the drug input–concentration relationship. The relation between concentration $C$ and slowing of median EEG frequency $E$ was modelled by the sigmoid function:

\[ E = E_0 - E_{\text{max}} \frac{C'}{C' + C'_0} \]

where $E_0$ represents the baseline median EEG frequency, $E_0 - E_{\text{max}}$ its maximum decrease, $C'_0$ the concentration at half maximum effect and $\gamma$ the steepness of the concentration–effect relationship.

As initial values, a baseline median EEG frequency of 9 Hz and a maximum decrease to 1 Hz were chosen. Concentration at half maximum effect was assumed to be 2.5 $\mu$g ml⁻¹ and $\gamma$ was set to 2.5, according to estimations from previously performed open-loop studies in volunteers. The interval of 2–3 Hz of median EEG frequency was used as the desired degree of EEG slowing.

A first update of the model parameters was performed after the initial period of 4 min. During the subsequent period of time, the following algorithm [4] was used: if median EEG frequency was within the range 2–3 Hz, propofol was administered by a B.E.T. (Bolus, Elimination, Transfer algorithm) infusion scheme [9,10] aiming at maintaining the current predicted concentration. If median EEG frequency was outside this range, the difference between the measured and predicted values served to adapt the

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Fig. 2. Mean (SD) time course of fractional EEG power during feedback control of propofol anaesthesia aiming at a median frequency in the range 2–3 Hz.

Model parameters (Appendix). On the basis of the updated parameters, a new infusion scheme was calculated for achieving and maintaining a concentration inducing a median EEG frequency of 2.5 Hz.

For hypothesis testing, the Wilcoxon and the
Mann–Whitney U tests were used. The non-parametric Levene test was used to compare the variance of different distributions.

RESULTS

During induction of anaesthesia, none of the volunteers showed signs of excitation. All were unresponsive to verbal commands during the feedback period. Eyelash reflex was always absent and, in general, corneal reflex was abolished.

Mean time to achieve the desired range of control was 10.4 (SD 4.6) min, during which propofol 256 (91) mg was administered. The average time course of median EEG frequency for the 11 volunteers is shown in figure 1. The distribution of all median EEG frequencies during the feedback period showed a mean of 2.53 Hz and a median of 2.45 Hz. The inter-quartile range was 1.5–3.6 Hz. The decrease of median EEG frequency was caused mainly by an increase of low frequency activity in the range 0.5–2 Hz (fig. 2). This activity increased from 11% to approximately 50% of total EEG activity at anaesthetic states associated with non-responsiveness to verbal commands.

The EEG values at baseline (B), during the feedback control period (F) and at recovery (R; orientation with respect to time and location), in addition to time to recovery (T) are shown in table I. Comparison of the EEG obtained during baseline and feedback showed a significant difference (P < 0.05) for all values except fractional power between 5–8 Hz and 13–32 Hz. It appears from table I that the interindividual variability of EEG values decreases from baseline to anaesthetic values. Testing for different variabilities (Levene test, P < 0.05) demonstrated significantly smaller variability during anaesthesia than during baseline, except for amplitude and fractional power between 0.5 and 2 Hz. The average amount of propofol required during the 2 h procedure was 1452 (262) mg. The cumulative amount of propofol delivered is shown in figure 3. The terminal slope of the cumulative dose curve is 10.2 (0.9) mg min⁻¹.

Comparison with methohexitone

The 11 volunteers in this study did not differ significantly with respect to age, body weight and height from the group of 11 volunteers studied in a previous feedback control investigation with methohexitone [4]; nor did each group differ with respect to baseline EEG parameters. However, a significant difference was observed in the EEG frequency distribution during anaesthesia, while median EEG frequency and amplitude did not differ between the groups. Compared with methohexitone, propofol increased activity in the frequency bands 0.5–13 Hz and 13–32 Hz and decreased activity in the frequency bands 2–5 Hz and 5–8 Hz. The ratio of cumulative doses of propofol required in this study and of methohexitone in the previous study is given in figure 4. The average ratio of methohexitone to propofol dose to maintain a median EEG frequency of 2.5 Hz was 0.72. The recovery time from stopping the infusion to orientation with respect to time and location was both more rapid and more
predictable with propofol than with methohexitone (17.9 (8.0) min and 40.2 (16.9) min, respectively).

**DISCUSSION**

Models can be used to derive dose regimens to induce and maintain a desired anaesthetic effect in the average patient. However, programmed drug administration may need some means of adjustment when applied to a specific subject under varying conditions of surgery. Population pharmacokinetics [11,12] may identify the influence of various anthropometric and physiological variables on the individual disposition of drugs. However, if the pharmacodynamic response can be measured continuously, it is a reasonable approach to use this information for adjustment of drug delivery.

Engineering sciences have developed a number of methods for the automatic control of processes. In this paper, we used model based, adaptive feedback control for administration of propofol. Using established pharmacokinetic–dynamic models, one can calculate programmed schemes of drug administration as a first approximation to the individual drug requirement. The controller has to identify subsequently only individual corrections to the suggested administration scheme. The adaptive feature of the controller was designed to compensate for different co-medications and time-varying events in surgical patients.

Our results show that, under the conditions of frequent random stimulation, the controller succeeds in maintaining anaesthesia (defined by non-responsiveness to verbal commands) by propofol administration. Given the target range of 2–3 Hz for median EEG frequency, the average median frequency of 2.53 Hz obtained shows that the controller works accurately, as has previously been shown also with methohexitone [4]. The precision in the present study was less than in the case of methohexitone. The interquartile range for the distribution of median EEG frequency lay between 1.5 Hz and 3.6 Hz for the propofol study and between 2 Hz and 3 Hz for methohexitone. However, our clinical impression did not indicate a less stable time course of anaesthesia, as judged by responsiveness to the various stimuli, in the case of propofol than in the case of methohexitone.

The residual α-activity was about 21 % and β-activity about 9 % of total EEG activity during feedback control (table I), compared with 16 % of residual α-activity and 6 % of β-activity in methohexitone anaesthesia. A more pronounced bimodal shape of the EEG power spectrum could account partially for the wider scatter of median EEG frequency during propofol anaesthesia. Other reasons (e.g. a steeper concentration–response curve, or hysteresis between dosing and effect) require more detailed investigation of the EEG of propofol and its relationship to dosing.

When comparing the EEG power distribution during baseline and recovery, we observed a significant decrease of α-activity and increase of β-activity, while the comparison of the baseline values with the anaesthesia period showed no significant changes in θ-activity (5–8 Hz) and β-activity. These findings suggest that the anaesthetic state induced by propofol is accompanied by a shift from α-activity to below 5 Hz, while
residual propofol effects, which might include states of light sedation, are characterized by β-
activation.

The relative potency of propofol, compared with methohexitone, was 0.72. This ratio calculated from cumulative dose requirements after the 20th min of methohexitone and propofol administration, after which time all volunteers of both groups had reached the desired range of control. This ratio may not necessarily apply to bolus doses. The average amount of methohexitone necessary to achieve the range 2–3 Hz of median EEG frequency was 192 (102) mg within a time of 9.6 (5.2) min, compared with propofol 253 (91) mg given within 10.4 (8.0) min, indicating, for that shorter period of time, a potency ratio of 0.76. Relative potencies expressed in terms of drug requirements are influenced by different quantities when estimated from bolus dose or from drug requirements at steady-state. In addition to concentration at the biophase, initial volume of distribution and its equilibration with the active site play an important role after bolus administration, while clearance is a factor to be considered when comparing drug requirements at steady-state. The relative potency of propofol and the average rate of infusion of propofol agree reasonably well with findings of Mackenzie and Grant [13]. To maintain general anaesthesia during regional anaesthesia in non-premedicated patients scheduled to undergo surgery of the lower limbs, they found a rate of infusion of 0.13 mg kg⁻¹ min⁻¹ for propofol and 0.089 mg kg⁻¹ min⁻¹ for methohexitone, corresponding to a rate of 9.1 mg min⁻¹ of propofol for a 70-kg patient and to a relative potency of 0.68. However, this study gave no data on recovery times for propofol and methohexitone.

Another study [14] of premedicated patients given either propofol or methohexitone to maintain general anaesthesia during surgery with regional blockade found maintenance doses of 0.103 mg kg⁻¹ min⁻¹ of propofol and 0.104 mg kg⁻¹ min⁻¹ of methohexitone, indicating a relative potency of 1. In agreement with the results of our study, the recovery time after propofol anaesthesia was less than 50% of the recovery time after methohexitone anaesthesia. The seemingly conflicting results of these studies emphasize the need for objective methods in defining drug requirement for maintaining anaesthesia. The feedback control approach of anaesthetic drug delivery is such a method, suited for both pharmacological research and therapy.

Feedback control methods in the clinical situation require a fail-safe system. The most important complication, when using the EEG, is sensor failure as a result of high frequency electrical interference. We believe that the pharmacokinetic–dynamic model used in constructing the controller could be a reasonable solution to this problem. In the case of a recognized sensor failure, the system can switch to the open-loop mode, during which the rate of drug administration is calculated on the basis of the updated model.

APPENDIX

ADAPTATION ALGORITHM

The pharmacokinetic–dynamic model used consisted of two formulae: a relation between drug input function \( I(t) \) and drug concentration \( C(t) \):

\[
C(t) = \int_0^t G(t-t') I(t') \, dt'
\]

(1)

and a relation between concentration \( C(t) \) and effect \( E(t) \):

\[
E = E_0 - E_{\text{max}} \frac{C}{C^* + C_0^*}
\]

(2)

whereby the function \( G(t) \) is given by the blood concentration after a bolus of unit dose, that is:

\[
G(t) = A \exp(-\alpha t) + B \exp(-\beta t)
\]

Inserting equation (1) into equation (2) immediately relates drug dosing \( I(t) \) to effect, and eliminates one parameter of the set of eight \( (A, \alpha, B, \beta, E_0, E_1, C_0, \gamma) \) because it depends only on the ratios \( A/C_0 \) and \( B/C_0 \) as a result of the scale invariance of equation (2) under the transformation \( (C_0, C_0') \rightarrow (\lambda C_0, \lambda C_0') \).

Given any desired effect \( E \), equation (2) may be inverted to give the desired concentration and equation (1) may subsequently be inverted to give the necessary drug input function.

A full adaptation algorithm requires an estimation of all seven parameters. This can be achieved only if the duration of the investigation is long enough to determine the largest half-life and the signal output is sensitive to all parameters, which requires in general a wide variation of concentration and effect. The present study has had the aim of maintaining the signal within a predefined band. Therefore we confined the parameters to be adjusted to \( A \) and \( B \). Such a choice allows adjustment of both initial volume of distribution (a major determinant of the subject’s response immediately after a bolus dose) and clearance (which has an important impact on the subject’s response to steady-state infusion).

The effect \( E \) may be regarded as a function of \( A \) and \( B \) and the drug input \( I(t) \):

\[
E = E(A, B, I(t))
\]

Denoting by \( A + \delta A \) and \( B + \delta B \) the true hybrid constants for an individual subject, the difference between measured and predicted effect (\( \Delta E \)) can be expanded in a Taylor series, as follows:

\[
E = E(A + \delta A, B + \delta B, I(t)) - E(A, B, I(t)) = (\delta E/\delta A)\delta A + (\delta E/\delta B)\delta B + ...
\]

(3)
In conjunction with the condition to minimize the expression $\delta A^2 + \delta B^2$, equation (3) was used to solve for $\delta A$ and $\delta B$. From the updated values, new microconstants were calculated that served to correct the drug input function.

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